General

Guideline Title

Clostridium difficile infection in adults and children.

Bibliographic Source(s)

University of Michigan Health System. Clostridium difficile infection in adults and children. Ann Arbor (MI): University of Michigan Health System; 2016 Dec. 29 p. [163 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
	Patient and Public Perspectives

	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▯	Study Selection
▮▮▮▮▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▯▯	Grading the Quality or Strength of Evidence
▮▮▮▯▯	Benefits and Harms of Recommendations
▮▮▮▮▯	Evidence Summary Supporting Recommendations
▮▮▯▯▯	Rating the Strength of Recommendations
▮▮▮▮▯	Specific and Unambiguous Articulation of Recommendations
▮▯▯▯▯	External Review
▮▮▮▮▮	Updating

Recommendations

Major Recommendations

Note from the University of Michigan Health System (UMHS) and the National Guideline Clearinghouse (NGC): The following guidance was current as of December 2016. Because UMHS occasionally releases minor revisions to its guidance based on new information, users may wish to consult the original guideline document for the most current version.

Note from NGC: The following key points summarize the content of the guideline. Refer to the original guideline document for additional information.

The strength of recommendation (I-III) and levels of evidence (A-E) are defined at the end of the "Major Recommendations" field.

Key Points for Adult Patients

Diagnosis

Definitive diagnosis of *Clostridium (C.) difficile* infection (CDI) requires either the presence of toxigenic *C. difficile* in stool with compatible symptoms, or clinical evidence of pseudomembranous colitis (see Table 2, Figure 4 in the original guideline document).
Once identified, CDI should be classified according to severity (see Table 3 in the original guideline document).
Although risk factors for CDI (see Table 1 in the original guideline document) should guide suspicion for CDI, testing should be ordered only when indicated (see Figure 1 in the original guideline document) *[IC]*.
Choice of test should be guided by a multistep algorithm for the rapid diagnosis of CDI (see Figure 2

in the original guideline document) *[IIC].*

Single-step polymerase chain reaction (PCR) testing (not part of the UMHS algorithm) occurs as part of the new Biofire test panel for gastrointestinal pathogens and should not be used if CDI is suspected *[IIIB]*. However, if *C. difficile* is detected as part of this panel and the patient's symptoms are compatible with CDI, then treatment is appropriate and additional testing is unnecessary *[IIC]*.

Patients who are asymptomatic, actively being treated or completed treatment for CDI with clinical improvement in symptoms, or have post-infectious irritable bowel syndrome after CDI should not undergo testing for CDI *[IIIC]*.

Treatment (see Figure 3 and Table 4 in the original guideline document)

Mild-Moderate CDI: Patient does not meet criteria for "severe" or "complicated" CDI

Metronidazole 500 mg by mouth (PO), three times daily (TID) for 10 to 14 days *[IIB]*.

OR

In patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy: vancomycin 125 mg PO four times daily (QID) for 10 to 14 days *[IB]*.

Severe CDI: Patients with white blood cell (WBC) count ≥15K, creatinine ≥1.5x baseline, age ≥65, absolute neutrophil count (ANC) ≤500, albumin ≤2.5, solid organ transplant (SOT)/bone marrow transplant (BMT) <100 days, chronic graft-versus-host-disease (GVHD) (BMT), treatment of rejection in the preceding 2 months (SOT), small bowel CDI, or inflammatory bowel disease

Vancomycin 125 mg PO QID for 10 to 14 days *[IA]*.

Complicated CDI: Patients with septic shock, ileus, toxic megacolon, peritonitis, or bowel perforation

Triple therapy = Vancomycin 500 mg by mouth, four times daily, metronidazole 500 mg intravenous (IV) every 8 hours, and vancomycin enema every 6 hours (in patients with ileus, bowel obstruction or toxic megacolon) *[IB]*.

Consult infectious diseases

Consult surgery to assist in management including possible surgical intervention (see Table 4, Figure 5 in the original guideline document).

Recurrent CDI: Recurrent symptoms and positive testing for toxigenic *C. difficile* within 8 weeks of prior episode

First recurrence:

Classify as "mild-moderate" "severe," or "complicated," and treat accordingly *[IC]*.

Second or multiple recurrences (third or more episode of CDI):

Consult infectious diseases

Vancomycin PO (dose, need for concurrent intravenous metronidazole/vancomycin enemas depends on disease classification as noted above) for 10 to 14 days then taper to 125 mg PO twice daily (BID) for 7 days, 125 mg PO daily for 7 days, and then pulse with 125 mg PO once every 2 to 3 days for 2 to 8 weeks *[IIC]*.

OR

Fidaxomicin 200 mg PO BID for 10 days (with approval from the infectious diseases consult service) *[IIE]*.

<u>Key Points for Pediatric Patients ≤18 Years of Age</u>

Diagnosis

The decision to test children for CDI is complicated given a high rate of asymptomatic carriage, especially in infants <12 months of age. Although risk factors for CDI should guide suspicion for CDI, testing should be ordered only when indicated (see Figure 1 in the original guideline document) *[IC]*. Indications and contraindications for testing pediatric patients are included in Figure 1, but testing is rarely indicated or recommended for infants <12 months *[IIC]* and consultation with pediatric infectious diseases (ID) is recommended. Children from 12 months to 36 months of age may be diagnosed with CDI if no alternative etiology for diarrhea is identified and with positive diagnostic testing *[IIC]*.

Definitive diagnosis of CDI requires either the presence of toxigenic *C. difficile* in stool with other symptoms, or clinical evidence of pseudomembranous colitis (see Table 2 in the original guideline document). Choice of test should be guided by a multistep algorithm for the rapid diagnosis of CDI (see Figure 2 in the original guideline document). Single-step testing (not part of the UMHS algorithm) occurs as part of the new Biofire test panel for gastrointestinal pathogens and should not be used if CDI is suspected *[IIIE]*. However, if *C. difficile* is detected as part of this panel and the patient's symptoms are compatible with CDI, then treatment is appropriate and additional testing is unnecessary *[IIC]*. Patients who are asymptomatic, actively being treated or completed treatment for CDI with clinical improvement in symptoms, or have post-infectious irritable bowel syndrome after CDI should not undergo testing for CDI *[IIIC]*.
Once identified, CDI should be classified according to severity (see Table 3 in the original guideline document). Certain pediatric conditions are associated with severe CDI and should be treated as such (see Table 3 in the original guideline document) *[IIC]*.

Treatment (see Figure 3 in the original guideline document for general strategy and Table 3 for pediatric-specific dosing recommendations)

Mild-Moderate CDI: Patient does not meet criteria for "severe" or "complicated" CDI

Metronidazole 7.5 mg/kg/dose PO QID for 10 days, maximum 500 mg/dose *[IIC]*.

OR

In patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy, or who fail to improve after 3 to 5 days of oral metronidazole therapy: vancomycin 10 mg/kg/dose PO QID, up to maximum 125 mg/dose x 10 days *[IIC]*.

Severe CDI: Pediatric patients with ≥2 lab criteria (WBC ≥15K, Cr ≥1.5x baseline, ANC ≤500, albumin ≤2.5) OR ANY high-risk condition with Hirschsprung's disease or other intestinal dysmotility disorder, neutropenia from leukemia or other malignancy, inflammatory bowel disease, SOT/BMT <100 days

Vancomycin 10 mg/kg/dose PO QID, up to maximum 125 mg/dose x 10 days *[IB]*.

Complicated CDI: Patients with septic shock, ICU admission within 2 days of CDI diagnosis, surgery related to CDI diagnosis, ileus, toxic megacolon, peritonitis, or bowel perforation

Triple therapy = vancomycin up to 500 mg PO QID, metronidazole 7.5 mg/kg/dose IV every 6 hours up to 500 mg/dose, and vancomycin enema 10-20 ml/kg/dose up to 1000 mL/dose every 6 hours of vancomycin 500 mg/L solution (if tolerated, 20 mL/kg/dose every 6 hours is preferred, however in patient with additional administration considerations, a minimum of 10 mL/kg/dose every 8 hours should be used) (in patients with ileus, bowel obstruction or toxic megacolon; bowel perforation is a contraindication to enema therapy) *[IC]*.

Consult pediatric infectious diseases

Consult pediatric surgery to assist in management including possible surgical intervention (see Table 4 in the original guideline document).

Recurrent CDI: Recurrent symptoms and positive testing for toxigenic *C. difficile* within 8 weeks of prior episode.

First recurrence:

Classify as "mild-moderate," "severe," or "complicated," and treat accordingly *[IC]*.

Second or multiple recurrences (third or more episode of CDI):

Consult pediatric infectious diseases

Vancomycin PO (dose, need for concurrent intravenous metronidazole/vancomycin enemas depends on disease classification as noted above) for 10 to 14 days then taper to 125 mg PO BID for 7 days, 125 mg PO daily for 7 days, and then pulse with 125 mg PO once every 2 to 3 days for 2 8 weeks to *[IIC]*.

OR

Fidaxomicin 16 mg/kg/dose BID, max 200 mg per dose, for 10 days *[IIC]*; pediatric ID approval is required for use.

Definitions

Levels of Evidence

- Systematic reviews of randomized controlled trials with or without meta-analysis
- Randomized controlled trials
- Systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
- Individual observational studies (case study/case series)
- Expert opinion regarding benefits and harm

Strength of Recommendation

- Generally should be performed
- May be reasonable to perform
- Generally should not be performed

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Indications and Contraindications for CDI Testing
- University of Michigan Health System Multistep Algorithm for the Rapid Diagnosis of *Clostridium (C.) difficile* Infection
- *C. difficile* Infection Treatment Algorithm Overview
- Operative Management Strategy for CDI

Scope

Disease/Condition(s)

Clostridium difficile infection

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide a brief overview of the epidemiology of, and risk factors for development of *Clostridium difficile* infection (CDI)
- To provide guidance regarding which patients should be tested for CDI, summarize merits and limitations of available diagnostic tests, and describe the optimal approach to laboratory diagnosis
- To review the most effective treatment strategies for patients with CDI including patients with recurrences or complications

Target Population

Adult and pediatric patients with a primary or recurrent episode of *Clostridium difficile* infection (CDI)

Interventions and Practices Considered

Diagnosis/Evaluation

Definitive diagnosis (laboratory testing, imaging)
Classification of disease severity (mild/moderate, severe, complicated)

Treatment

Antimicrobial treatment based on severity
    Metronidazole
    Vancomycin
    Fidaxomicin
Consult with infectious diseases
Consult with surgery

Major Outcomes Considered

- Sensitivity/specificity of diagnostic tests
- Infection rate
- Cure rate
- Recurrence rate
- Time to improvement
- Mortality
- Adverse effects of medication

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used for most of the search topics, except for the searches on suppurative thrombosis, endocarditis, and vascular infection. The search below is identified as Main in the Methodological Appendix (see the "Availability of Companion Documents" field). Because the appropriate indexing terms either do not exist or were applied inconsistently, the main search uses keywords in addition to MeSH terms to arrive at the following main strategy.

> exp *Clostridium difficile/ or exp *enterocolitis/ or exp *Clostridium Infections/
> exp *Hirschsprung Disease/
> limit 2 to "all child (0 to 18 years)"
> 1 or 3
> exp animals/ not (exp animals/ and humans/)
> 4 not 5
> limit 6 to (english language and yr="2013 -Current")
> remove duplicates from 7. The searches on suppurative thrombosis, endocarditis, and vascular infection used the first 3 searches of the main search strategy. The MEDLINE In-Process search was based entirely on keywords.

Results were limited to: English, and 2013 to present. The Main search retrieved 893 references. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added, the base results are as follow:

> C-Diff Guidelines, total results were 8
> C-Diff Clinical Trials, total results were 27
> C-Diff Cohort Studies, total results were 59

The search was conducted in components each keyed to a specific causal link in a formal problem structure. The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Search details and evidence tables are available in the methods companion (see the "Availability of Companion Documents" field).

Number of Source Documents

A total of 440 articles were identified, and 163 studies were identified as best evidence.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

> Systematic reviews of randomized controlled trials with or without meta-analysis

Randomized controlled trials
Systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
Individual observational studies (case study/case series)
Expert opinion regarding benefits and harm

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Best Evidence Identified and Organized into Evidence Tables

The best evidence for the current guideline is synthesized into 23 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 127 publications. The tables themselves are contained in Section VI of the Methodological Appendix (see the "Availability of Companion Documents" field), and present the synthesis of the best evidence identified.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline recommendations were based on prospective randomized controlled trials (RCTs) if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

Generally should be performed
May be reasonable to perform
Generally should not be performed

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, Department of Surgery, Infectious Diseases Division, Gastroenterology Division. Pediatrics and Communicable Diseases and the Division of Pediatric Infectious Diseases. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- A recent retrospective study showed that, for patients where the *Clostridium difficile* infection (CDI) episode was a first or greater recurrence, prophylactic vancomycin reduced the risk of recurrent CDI by nearly 50% when on other antibiotics.
- A prospective case series of patients with multiple recurrences of CDI found that daily administration of kefir (a probiotic yogurt drink) in combination with a staggered and tapered oral vancomycin or metronidazole regimen achieved a treatment success rate of 84%.
- In a randomized, double-blind, placebo-controlled Phase II trial, addition of two neutralizing monoclonal antibodies against CDI toxins A and B to standard therapy did not impact the initial infection course but did significantly reduce infection recurrence.
- Based on a wealth of data from case reports, systematic reviews, and clinical trials, fecal microbiota transplantation (FMT) appears quite effective for recurrent CDI with cure rates exceeding 85% to 90% in most studies.
- In patients who have severe, complicated (fulminant) CDI and clinical deterioration despite maximal medical therapy, surgery may confer mortality benefit.

Potential Harms

- There are circumstances when false-negative results can occur with enzyme immunoassay (EIA) testing alone. Immunocompromised patients with symptoms suggestive of *Clostridium difficile* infection (CDI) (colitis on imaging, ileus with minimal stool production, and/or white blood cell count [WBC] >15,000 cells/μL with diarrhea) and patients receiving empiric therapy at the time of diagnosis are at risk for a false-negative EIA test.
- A recent retrospective study showed that, for patients where the CDI episode was a first or greater recurrence, prophylactic vancomycin reduced the risk of recurrent CDI by nearly 50% when on other antibiotics. Potential downsides of this strategy include selection for resistant organisms such as vancomycin-resistant *Enterococcus*, onset or worsening of antibiotic-associated diarrhea, and additional expense.
- Caution should be exercised with use of fecal microbiota transplantation (FMT) in patients with inflammatory bowel disease (IBD). Those who undergo FMT for CDI may be at increased risk of IBD flare, fever, and/or elevation in inflammatory markers.

- In advanced fulminant CDI, surgical mortality can be up to 80% (range 19% to 80%).
- Delayed surgical intervention may result in increased morbidity and mortality. Prior studies indicate higher mortality rates if surgical intervention occurred after evidence of end-organ failure (e.g., intubation for respiratory failure, vasopressor therapy for hemodynamic instability, or acute renal failure).

Contraindications

Contraindications

- Contraindications for *Clostridium difficile* infection (CDI) testing
  - Asymptomatic
  - Recently finished therapy (test of cure)
  - While on therapy
  - Mild post-infectious irritable bowel syndrome (IBS) (relative contraindication - use clinical judgment)
  - Recently finished therapy and symptoms have resolved (test of cure)
  - Infants under 12 months of age generally should not be tested (for exceptions, see Figure 1 in the original guideline document).
  - Caution is advised in ordering and interpreting testing in children 12 to 36 months of age and should be limited to children with risk factors for acquiring CDI (see Table 1 in the original guideline document) and no alternative etiology for diarrhea or ileus identified.
- Colonoscopy is contraindicated, especially for diagnostic purposes, in patients with hemodynamic instability or with significant risk for bowel perforation (e.g., fulminant colitis, recent bowel surgeries, bowel obstruction).
- Bowel perforation is a contraindication to enema therapy.
- Fecal microbiota transplantation (FMT) is contraindicated in patients with complicated CDI.
- Partial colectomy is contraindicated.
- For pediatric patients with prolonged or recurrent CDI, metronidazole should not be used for chronic therapy due to possible neurotoxicity.

Qualifying Statements

Qualifying Statements

These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

University of Michigan Health System. Clostridium difficile infection in adults and children. Ann Arbor (MI): University of Michigan Health System; 2016 Dec. 29 p. [163 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Dec

Guideline Developer(s)

University of Michigan Health System - Academic Institution

Source(s) of Funding

The development of this guideline was funded by the University of Michigan Health System.

Guideline Committee

Clostridium difficile Infection Guideline Team

Composition of Group That Authored the Guideline

Team Leads: Tejal N Gandhi, MD, Infectious Diseases; Krishna Rao, MD, Infectious Diseases

Team Members: Gregory Eschenauer, PharmD, Pharmacy; John Y Kao, MD, Gastroenterology; Andrea H Kim, MD, Internal Medicine; Lena M Napolitano, MD, Surgery; F. Jacob Seagull, PhD, Learning Health Sciences; David M. Somand, MD, Emergency Medicine; Kathleen B To, MD, Surgery; Alison C Tribble, MD, Pediatric Infectious Diseases; Amanda M Valyko, MPH, CIC, Infection Control; Michael E Watson, Jr., MD, PhD, Pediatric Infectious Diseases

Consultants: Meghan A Arnold, MD, Pediatric Surgery; Daniel H Teitelbaum, MD, Pediatric Surgery; Laraine Lynn Washer, MD, Infection Diseases

Inpatient Clinical Guidelines Oversight: Megan R Mack, MD; David H Wesorick, MD; F Jacob Seagull, PhD

Financial Disclosures/Conflicts of Interest

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

No relevant personal financial relationships with commercial entities: Meghan A Arnold; Gregory Eschenauer, PharmD; Tejal N Gandhi, MD; John Y Kao, MD; Andrea H Kim, MD; Lena M Napolitano, MD; Krishna Rao, MD; F Jacob Seagull, PhD; David M Somand, MD; Daniel H Teitelbaum, MD; Kathleen B To, MD; Alison C Tribble, MD; Amanda M Valyko; Laraine Lynn Washer, MD; Michael E Watson Jr, MD, PhD

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the University of Michigan Health System Web site

Availability of Companion Documents

The supplemental methodological appendix is available from the University of Michigan Health System (UMHS) Web site.

A continuing medical education self-study activity is available from the UMHS Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 18, 2017. The information was verified by the guideline developer on September 19, 2017.

This NEATS Assessment was completed by ECRI Institute on August 8, 2017. The information was verified by the guideline developer on September 19, 2017.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.